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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,723	06/26/2003	Andrew R. Marks	19240-594-US1	6915

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WilmerHale/Columbia University
399 PARK AVENUE
NEW YORK, NY 10022

EXAMINER	
LI, RUIXIANG	
ART UNIT	**PAPER NUMBER**
1646	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/608,723	MARKS, ANDREW R.	
	Examiner	Art Unit	
	Ruixiang Li	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,13,15-18 and 25-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,13,15-18 and 25-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/20/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The amendment filed on 12/06/2006 has been entered. Claims 1, 4, 6, 13, 16, 18, 33, and 38 are amended. Claims 7-12 and 19-24 are canceled. Claims 1, 3-6, 13, 15-18, 25-42 are pending and under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Withdrawn Objections and/or Rejections

The rejection of claims 4, 5, 16, 17 28, 29, 31, and 32 under 35 U.S.C.§112, first paragraph for scope of enablement, is withdrawn in view of amended claims.

The rejection of claims 4, 5, 16, 17, 28, 29, 31, and 32 under 35 U.S.C.§112, first paragraph for written description is withdrawn in view of amended claims.

Claim Rejections under 35 USC § 112, 1st paragraph

The rejection of claims 33-36 and 48-81 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treating atrial tachyarrhythmia or inhibiting the onset of atrial tachyarrhythmia in a human subject comprising administering to the human subject a therapeutically effective amount of JTV-519, does

not reasonably provide enablement for such a method of employing a genus of N-substituted derivative of 1,4-benzothiazepine, *which enables FKB12.6 to bind to PKA-phosphorylated type 2 ryanodine receptor channels* in the human subject's heart. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claims.

Applicants argue that one of skill in the art could make other N-substituted derivative of 1,4-benzothiazepine without undue experimentation. Similarly, one of skill in the art could administer such N-substituted derivative of 1,4-benzothiazepine to human subjects without undue experimentation.

Applicants' argument has been fully considered, but is not deemed to be persuasive for the following reasons. First, it is noted that the rejection of claims 4, 5, 16, 17 28, 29, 31, and 32 under 35 U.S.C.§112, first paragraph for scope of enablement has been withdrawn in view of amended claims. Secondly, claims 33-36 are drawn to a method for treating a human subject afflicted with atrial tachyarrhythmia comprising administering to the human subject a therapeutically effective amount of an agent, *which enables FKBP12.6 to bind to PKA-phosphorylated type 2 ryanodine receptor (RyR2) channels* in the human subject's heart, where the agent is a derivative of 1,4-benzothiazepine, whereas claims and 38-41 are drawn to a method for inhibiting the onset of atrial tachyarrhythmia in a human subject comprising administering to the

human subject a prophylactically effective amount of an agent, *which enables FKBP12.6 to bind to PKA-phosphorylated type 2 ryanodine receptor (RyR2) channels* in the human subject's heart, where the agent is a N-substituted derivative of 1,4-benzothiazepine.

However, the specification discloses that a single agent, JTV-519, enables FKBP12.6 to bind to PKA-phosphorylated RyR2 (page 93 of the specification). The specification also teaches a number of agents that inhibits PKA phosphorylation of RyR2 receptor or dissociation of a FKBP12.6 from RyR2 receptor (Reiken et al., *Circulation* 104:2843-2848, 2001; Doi et al., *Circulation* 105:1374-1379, 2002; Yano et al., *Circulation* 107:477-484, 2003). However, the specification fails to provide sufficient guidance and working examples on how to make and use other agents that enable FKBP12.6 to bind to PKA-phosphorylated RyR2. The prior art does not provide compensatory structural or correlative teachings to enable one skilled in the art to make the genus of N-substituted derivative of 1,4-benzothiazepine that enable FKBP12.6 to bind to PKA-phosphorylated RyR2. In view of the complexity of the nature of the work related to treating heart disease such as atrial tachyarrythmia, it is unpredictable whether a N-substituted derivative of 1,4-benzothiazepine has the property of enabling FKBP12.6 to bind to PKA-phosphorylated RyR2. Therefore, it would require undue experimentation for one skilled in the art to make and use the claimed invention commensurate in scope with the claims.

Claim Rejections under 35 USC § 112, 1st paragraph (New matter)

Claims 1, 3-5, 13, 15-17, 25, 26, 28, 29, 31-36, 38-41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 3-5, 13, 15-17, 25, 26, 28, 29, 31-36, 38-41 recite "N-substituted derivative of 1,4-benzothiazepine". There is no support for such a subgenus in the original disclosure.

Claim Rejections Under 35 U. S. C. § 103 (a)

The rejection of claims 1, 3-6, 13, 15-18, and 25-42 under 35 U.S.C. 103(a) as being unpatentable over Nakaya et al. (*British Journal of Pharmacology*, 131: 1363-1372, 2000) is maintained.

In the 3rd paragraph of page 10 of Applicants' response filed on 12/06/2006, Applicants argue that Nakaya fails to mention any effect of JTV-519 on AFT. Applicants' argument has been fully considered, but is not deemed to be persuasive because while Nakaya et al. do not explicitly teach the effect of JTV-519 on AFT, Nakaya et al. do teach an inhibitory effect of JTV-519 on experimental atrial fibrillation in Langendorff-perfused guinea-pig hearts. Nakaya et al. teach that addition of JTV-519 (1 uM) inhibited the

induction of atrial fibrillation by prolonging monophasic action potential and effective refractory period (see, e.g., abstract).

In the 4th paragraph of page 10 of Applicants' response filed on 12/06/2006, Applicants argue that the induction of atrial fibrillation by high doses of carbachol in combination with rapid electrical pacing represents an artificial in vivo model which is not representative of pathophysiologic AF mechanisms in vivo. Applicants argue that the teachings of Nakaya et al. fall short of suggesting that JTV-519 is useful for treating physiologic atrial fibrillation in vivo, whether in guinea pigs, humans, or in other animals.

Applicants' argument has been fully considered, but is not deemed to be persuasive because the experimental atrial fibrillation in guinea-pig hearts is a art accepted model, as judged by the fact that the publication of Nakaya et al. is a peer-reviewed article. There is no evidence on the record showing that the model of atrial fibrillation in guinea-pig hearts used by Nakaya et al. is irrelevant to the study of atrial fibrillation in animals including humans. Moreover, Nakaya et al. clearly state that JTV-519, a well-known cardioprotective drug before the filing date of the instant application (see, e.g., Introduction section of the publication), may be useful for the treatment of atrial fibrillation in patients with ischaemic heart disease (see, e.g., Abstract). Furthermore, additional studies in the prior art using other models, such as a dog (Yano et al., Circulation 107:477-484, January 28, 2003), validate the research of Nakaya et al.

Applicants, citing certain statements from the publication of the Nakaya et al, argue that one cannot conclude from Nakaya et al whether or not JTV-519 would inhibit AF in animals in vivo. Applicants' argument has been fully considered, but is not deemed to be persuasive. The examiner has the difficulty in understanding why Applicants argue that JTV-519 insignificantly prolonged APD90 in the absence of any muscarinic agent, such as carbachol (see, Fig. 1A). In examiner's viewpoint, the result illustrates the physiological effect of JTV-519 on the APD90 because an ideal drug is not expected to prolong the APD in the control condition, while prolonged the APD in the pathological condition. Nakaya et al. demonstrate that JTV-59 reversed the carbachol-induced action potential shortening in a concentration-dependent manner. Moreover, CCh-induced shortening of APD90 was also reversed (Fig. 1B; top of right column of page 1365).

In the 2nd paragraph of page 11 of Applicants' response filed on 12/06/2006, Applicants argue that because Nakaya et al. fail to show that JTV-519 can be used to treat atrial fibrillation in vivo, Nakaya et al. provide no reasonable expectation that 1, 4, benzothiazepine derivatives could successfully be used to treat pathophysiological (non-carbachol-induced) atrial fibrillation.

Applicants' argument has been fully considered, but is not deemed to be persuasive because Nakaya et al. clearly teach that JTV-519 exerts antiarrhythmic effects against atrial fibrillation and may be useful for the treatment of patients with atrial fibrillation (see, e.g., abstract) or the prevention of atrial fibrillation in patients with ischaemic heart

disease (bottom of right column of page 1370). At the time the instant application was filed, JTV-519, a well-known cardioprotective drug (see the introduction section of the publication of Nakaya et al.), was known to prevent the amount of RyR-bound FKBP12.6 from decreasing, to reduce the abnormal Ca2+ leak through the RyR, and to prevent dog left ventricular remodelling, leading to less severe in heart failure (Yano et al., Circulation 107:477-484, January 28, 2003). Therefore, the teachings of Nakaya et al. provide reasonable expectation that JTV-519 could successfully be used to treat atrial fibrillation in a patient, including a human patient.

In the 3rd paragraph of page 11 of Applicants' response filed on 12/06/2006, Applicants argue that it would not be obvious from Nakaya et al. that JTV-519 could be used to treat atrial fibrillation in humans. This is not persuasive because in view of the teachings of Nakaya et al, it would have been obvious to one having ordinary skill in the art at the time the invention was made to treat a human subject afflicted with atrial tachyarrhythmia by administering to the human subject a therapeutically effective amount of JTV-519 with a reasonable expectation of success. It is a logical and obvious step for one of skill in the art to treat a human subject after a drug is tested successfully in an animal model.

Beginning at the 4th paragraph of page 11 of Applicants' response filed on 12/06/2006, citing the reference of Wang et al., Applicants argue that animal tissues differ significantly from human tissues both in their electrophysiological characteristics

relevant for arrhythmia mechanisms and their sensitivity to antiarrhythmic drugs. Applicants argue that Wang et al. specifically found that the action of antiarrhythmic drugs in guinea pigs is not necessarily representative of their actions in humans.

Applicants' argument has been fully considered, but is not deemed to be persuasive because Wang et al. merely studied the effects of two antiarrhythmic drugs, flecainide and quinidine on action potentials in tissues of humans, dogs, rabbits, and guinea pigs. The two drugs are structurally unrelated to JTV-519. Thus, the conclusion may not be true for JTV-519. Secondly, Wang et al. did not study the difference of the effects of the two drugs on atrial fibrillation in humans, dogs, rabbits, and guinea pigs. Thus, their conclusion does not apply to the study of Nakaya et al, where the antiarrhythmic effects of JVT-519 were studied in guinea-pig hearts.

Moreover, Wang et al. compared the effects of equimolar concentrations of flecainide and quinidine (see, e. g, Abstract) on action potentials in tissues of various species. While human tissues were more sensitive than the tissues of dogs, rabbits, and guinea pigs to the effects of flecainide and quinidine, the teachings of Wang et al. do not show that flecainide and quinidine would not exert an effect in the tissues of dogs, rabbits, and guinea pigs. In fact, Wang et al used twice the concentration of flecainide and quinidine in guinea pigs, rabbits, and dogs compared with human tissue to achieve a pharmacologic response in a similar range (the 3rd paragraph of page 280). Thus, according to the teachings of Wang et al., it seems that if a tissue in a guinea pig is

sensitive to an antiarrhythmic drug, a human tissue would be more sensitive to the drug. In addition, Wang et al. do not teach, in any way, that an antiarrhythmic drug, JTV-519 that exerts antiarrhythmic effect against atrial fibrillation in guinea-pig hearts is not effective in a human patient.

Furthermore, since the paper of Nakaya et al. was published 10 years after the paper of Wang et al, and Nakaya et al studied the effect of JTV-519 on experimentation atrial fibrillation in guinea-pig hearts, the reference of Nakaya et al. represents a closer art to the present invention than the paper of Wang et al.

Finally, the instant specification merely discloses that a single agent, JTV-519, enables FKBP12.6 to bind to PKA-phosphorylated RyR2 (page 93 of the specification). There is no disclosure of an effect of JTV-519 on experimental atrial fibrillation in any animal models. Thus, Applicants' argument appears to say that the instantly claimed methods are not enabled.

In the 3rd paragraph of page 12 of Applicants' response filed on 12/06/2006, Applicants argue that because Nakaya et al. fail to provide data from animals other than guinea pigs and provide no data from established large animal models of atrial fibrillation, Nakaya et al. provide no reasonable expectation that JTV-519 or other 1, 4 benzothiazepine derivatives could successfully be used to treat atrial fibrillation in humans. This is found to be persuasive for the reasons above. In addition, the examiner

points out the fact that there is no disclosure of an effect of JTV-519 on experimental atrial fibrillation in any animal models. At the time the instant application was filed, it was know in the art that the development of heart failure is tightly correlated with a decrease in the stoichiometric ratio for FKBP12.6 binding to the ryanodine receptor in the sarcoplasmic reticulum and that JTV-519 reverses this pathogenic process (see, e.g., Abstract of paper of Yano et al., Circulation 107:477-484, January 28, 2003).

For the reasons above, the rejection of claims 1, 3-6, 13, 15-18, and 25-42 under 35 U.S.C. 103(a) as being unpatentable over Nakaya et al. (*British Journal of Pharmacology*, 131: 1363-1372, 2000) is maintained.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ruixiang Li whose telephone number is (571) 272-0875. The examiner can normally be reached on Monday through Friday from 8:30 am to 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached on (571) 272-0835. The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, please contact the Electronic Business Center (EBC) at the toll-free phone number 866-217-9197.

Ruixiang Li

Ruixiang Li, Ph.D.
Primary Examiner
February 15, 2007

RUIXIANG LI, PH.D.
PRIMARY EXAMINER